TRANSMITTAL LETTER (General - Patent Pending)	Docket No. S&B-C161

In Re Application Of: NANA K. AYISI

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/978,593	October 18, 2001	Ulrike Winkler	30132	1648	5237

Title: **ANTIVIRAL AND ANTIBACTERIAL ACTIVITIES OF EXTRACTS FROM EIGHT PLANTS**

COMMISSIONER FOR PATENTS:

Transmitted herewith is:

Appellant's Reply Brief Under 37 C.F.R. 41.41(a)(1)

Applicant submits herewith an Appellant's Reply Brief , in triplicate, in response to the Examiner's Answer mailed on November 29, 2005.

in the above identified application.

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Dated: **January 26, 2006**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 09/978,593	Confirmation No.	5237
Applicant	: Nana K. Ayisi		
Filed	: October 18, 2001		
TC/A.U.	: 1648		
Examiner	: Ulrike Winkler		
Docket No.	: S&B-C161		
Customer No.	: 30132		

APPELLANT'S REPLY BRIEF UNDER 37 C.F.R. 41.41(a)(1)

Commissioner for Patents
Alexandria, VA 22313-1450
U.S.A.

Dear Sir:

The following is the Appellant's Reply Brief, submitted in triplicate and under the provisions of 37 C.F.R. 1.192.

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I. Real Party in Interest

The real party in interest in the application is the Applicant.

II. Related Appeals and Interferences

There are no related appeals and interferences.

III. Status of Claims

Claims 1 to 19, 21 and 23 to 30 are cancelled in the application.

Claims 20, 22, 31 and 32 are rejected.

IV. Status of Amendments

No amendments have been made subsequent to the final action of April 19, 2005.

V. Summary of Claimed Subject Matter

The invention is directed to novel methods of inhibiting the cytopathic effects of a virus in a virus-infected cell by contacting the cell with an effective amount of an extract from *Ocimum gratissimum*.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 20, 22, 31 and 32 satisfy 35 U.S.C. §112, first paragraph.

2. Whether claims 20 and 31 are unpatentable under 35 U.S.C. §102(b) in view of El-Said *et al.* (Planta Medicine, 1969), as evidenced by the Merck Manual (Ed. Beers *et al.*, Published by Merck Research Laboratories, Whitehouse Station, N.J. (1999) pp. 1293-1296, 1303-1306, 1312-1323, 2320-2324 and 2341-2343).

VII. Argument

Issue 1. - 35 USC §112, 1st paragraph

The Examiner maintains that the specification while being enabling for inhibiting HIV viral replication in Vero cells and in Molt4 clone 8 cells with an extract of *Ocimum gratissimum*, does not however reasonably provide enablement for the *Ocimum gratissimum* extract to inhibit HIV viral replication in a mammal or in any other cell line.

The arguments set forth in the Examiner's Answer of November 29, 2005 (Answer) have been considered, however Appellant disagrees. Alternatively, it is submitted that the claims satisfy the enablement requirement of 35 U.S.C. §112, 1st paragraph in view of the following comments.

(i) Therapeutic effect of Ocimum gratissimum.

In Appellant's Appeal of August 26, 2005, reference was made to *In re Borokowski* 422 F.2d 904, 909, 164 USPQ 642, 645 (CCPA 1970), to highlight that the Examiner's analysis is improper as to what the claimed invention is, i.e. a method of inhibiting the cytopathic effects of a virus in a virus-infected cell by contacting the cell with an effective amount of an extract from *Ocimum gratissimum*.

In reply, the Examiner submits that Office personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure, citing *In re Morris*, 127 F.3d 1048, 104-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) as the authority for her proposition.

In particular, the Examiner states the following:

> ...There is insufficient guidance and objective evidence that such teachings would be indicative of the effect of *O. gratissimum* in vivo, i.e. in an individual; wherein it would be predictable to one of skill in the art to use the method in order to treat

HIV viral infection in any individual...clinical correlation is generally lacking. [Emphasis added.]

...inhibiting the replication/infection of a virus in vitro with a compound would not provide evidence that the compound would inhibit the intact virus from infecting its target cell in vivo...Therefore, the use of in vitro tests is not an acceptable predicator of in vivo activity when claiming treatments to HIV. [Emphasis added.]

...In this instance interpreting the claims as including treatment in a patient does not require a study of the disclosure. [Emphasis added.]

...There is no showing that sufficient amount of the composition can be giving [sic] to the HIV infected patient to effectuate a treatment without being lethal to the patient." [Emphasis added.]

Appellant maintains that the Examiner's approach to determining the enablement requirement under 35 U.S.C. §112 is improper in view of the invention claimed and described in the instant application, i.e. a novel method of inhibiting the cytopathic effects of a virus in a virus-infected cell by contacting the cell with an effective amount of an extract from *Ocimum gratissimum*. Further, based on the description and examples provided in the specification, a skilled person would be able to make and practice the invention without undue experimentation.

However, the Examiner asserts that the claims are to be given their broadest reasonable interpretation and that "a study of the disclosure is not required" to arrive at her interpretation of the claimed invention, i.e. in the "treatment of HIV in a patient" [emphasis added] . Appellant respectfully submits that the enablement requirement of 35 U.S.C. §112 does not permit such an approach to interpreting the claims. It has long been established that the enablement requirement of 35 U.S.C. §112 requires that the scope of the claims must bear a reasonable correlation to the

scope of enablement provided by the specification. The disclosure in the specification is the best source of support to illustrate the breadth of the claims.

Furthermore, Appellant refers to *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985) in which the CAFC was confronted with determining whether the Board erred in finding whether a Japanese priority application contained sufficient disclosure to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. The CAFC held that Iizuka's priority Japanese patent application disclosed sufficient information to enable one skilled in the art to use the invention under 35 U.S.C. §112, first paragraph. It was also determined that since the claimed invention was directed to a pharmacological activity, and not a specific human therapeutic use, the CAFC agreed with the Board that the applicant's failure to disclose a dosage range was not fatal to enable the invention. Specifically, the CAFC ruled that one skilled in the art, without inventive skill or undue experimentation, could determine the proper dosage ranges for the claimed invention. The CAFC also made it clear that its enablement analysis would have been different if Iizuka had claimed a therapeutic use rather than a pharmacological activity for the compounds. It is settled law that a specification must enable the claimed invention. Therefore, the quanta of evidence sufficient to meet the enablement threshold for pharmacological claims is different than for pharmaceutical (human therapeutic) claims.

Further, it is improper for the Examiner to make a rejection under 35 U.S.C. §112, first paragraph for lack of evidence to show safety or degree of efficacy of a compound in the treatment of humans, as these criteria are not within the statutory requirements of the patent law.[1]

(ii) Correlation of in vitro testing to in vivo efficacy.

(a) Sandström et al. reference.

Appellant previously argued that the Examiner's reliance on the teachings of the Sandström *et al.* reference is misplaced in concluding whether *in vitro* testing is predictive of *in vivo* efficacy. In

1 *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994): "Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."

reply, the Examiner contends that the Sandström *et al.* reference was cited to bolster the argument that *in vitro* effects cannot be extrapolated to *in vivo* HIV therapies and not for the purpose of showing any kind of structural relatedness of AZT or suramin to the extract of *Ocimum gratissimum.*

Appellant does not dispute whether the Sandström reference was cited to show any structural relatedness of AZT or suramin to the *Ocimum gratissimum* extract. Rather, Appellant argues that the lack of predictability of *in vitro* testing to *in vivo* efficacy discussed in Sandström *et al.* was determined solely on the basis of results for suramin and AZT. Suramin, as compared to numerous other anti-viral compounds, exert their effects through different modes of action (i.e. see Sandström *et al.*, page 374, Table 1. Potential points of attack in the HIV replication cycle). Therefore, the reference is unreliable to show that *in vitro* testing is not predictive of *in vivo* efficacy for all anti-viral agents. Further, the Examiner has not given full consideration to all the facts and information provided in this reference. More particularly, the Sandström reference describes problems specific to the properties of suramin that make predictions of its *in vivo* efficacy difficult. In discussing suramin as an anti-viral compound in AIDS therapy, Sandström states that the high protein binding of this compound "makes predictions from *in vitro* experiments difficult." (See the paragraph bridging pages 375-376.) Approximately 99.7% of suramin was bound to plasma proteins and that urinary excretion accounted for elimination of most of the drug.

Initially, Mitsuya *et al.*[2] demonstrated in 1984 that suramin could protect human T-cells against the infectious and cytopathic effects of HIV *in vitro*. However, Mitsuya *et al.* clearly state that the *in vitro* results reported in the paper provide a rationale for a "carefully-monitored experimental trial" of this anti-viral compound in patients with AIDS to determine whether suramin does inhibit HIV replication *in vivo*. Thus, even though *in vitro* efficacy of suramin against HIV infected human cells was established *in vitro*, the researchers were nevertheless

2 Mitsuya H, Matsushita S, Yarchoan R, and Broder S. 1984. *Protection of T Cells Against Infectivity And Cytopathic Effect of HTLV-III In Vitro.* Princess Takamatsu Symp. 15:277-88.

unwilling to predict that such *in vitro* work provided a basis to conclude that this compound would have *in vivo* efficacy.

Accordingly, Applicant submits that the Examiner's reliance on the teachings of Sandström to be misplaced because the distinctive properties of suramin made predictability of *in vivo* activity from *in vitro* testing difficult which, in absence of evidence to the contrary, are not relevant to the *Ocimum gratissimum* extract.

(b) Age of references.

The Examiner further submits that Appellant's argument that the Sandström *et al.* reference (1987) is not relevant art in the rapidly developing HIV field is not persuasive, stating:

> Although, there have been many discoveries in the past 20 years regarding HIV, the observations made by references early in the art are still relevant for what the references teach. In this instance the reference was cited for the teaching that suramin effects in vitro could not be used to extrapolate the effect of suramin in a patient...The argument that the art has develop [sic] significantly from that time period is not relevant to the observation that in vitro assays cannot predict in vivo results.

Appellant does not dispute that early references can still be relevant for what they teach, even in a rapidly developing field. However, in this instance, Sandström *et al.* is only relevant for discussing suramin as an anti-viral compound in AIDS therapy in relation to problems specific to the properties of suramin that make predictions of its *in vivo* efficacy difficult. On the other hand, Sandström is not relevant or reliable for predictions of *in vitro/in vivo* correlation concerning other anti-viral agents.

The Examiner further argues that advances in the field of HIV and AIDs related treatments over the course of 14 years is <u>not</u> relevant to the observation that *in vitro* testing cannot predict *in vivo*

results. Appellant respectfully disagrees and submits that the Examiner's position in this respect is unreasonable. In over a decade, research and development has been responsible for key advances in HIV research that have changed our understanding of the management, and possibly the outcomes, of HIV disease. Our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission have all been changed as a result of numerous publications that add to the increasing pool of scientific knowledge. Knowledge gained from these studies has benefited researchers to create new agents and vaccines to combat HIV infection.

Further, Appellant has referred to several publications spanning more than a decade of research subsequent to the teachings of Sandström *et al.* which confirm that *in vitro* results can be predictive of the clinical situation in the treatment of HIV (see page 7 of Appellant's Appeal Brief).

(iii) Working examples and guidance in the specification.

Appellant previously argued that art-accepted *in vitro* model correlates to an *in vivo* model and that a rigorous or invariable exact correlation between the *in vitro* and *in vivo* model is not required (MPEP §2164.02; *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). In reply, the Examiner states:

> ...the Office has cited evidence that the tissue culture based assay model does not correlate to the effect of the drug in the patient. The Office has shown that there is no correlation between an in vitro model and an in vivo effect for the treatment of HIV in a person because the medicament may not be able to be given at high quantities to be an effective treatment and it may not even be effective at doses that are toxic to a person. If a compound is toxic at concentrations that inhibit HIV replication in the patient it cannot be considered a therapy. [Emphasis added.]

Again, the Examiner refers to Sandström *et al.* for establishing that *in vitro* data cannot be extrapolated to *in vivo* HIV therapies. She further adds that vaccines developed for preventing viral entry into cells have been found effective in the *in vitro* setting, but not in the clinical setting. It is noted, however, that no reference has been cited to substantiate this assertion.

As a first issue, Appellant points out that the Examiner consistently argues that the *Ocimum gratissimum* extract may not be able to be given at high quantities to be effective and/or non-toxic to a person undergoing HIV treatment and therefore, cannot be considered a therapy. However, the Examiner is reminded that the claims define a method for inhibiting the cytopathic effects of a virus in a cell, and not a therapeutic use in the treatment of HIV in a patient. Further, there is nothing in the patent statute, which grants the Examiner the authority to require an applicant to prove that the compounds or other materials which it is claiming to have a beneficial pharmacological activity are safe, effective and reliable for use with humans. The Examiner's position appears to be that where an invention embodies a potential use as a human therapeutic, yet the application discloses *in vitro* data in support of such utility, the claims are rejected as unpatentable under 35 U.S.C. §112, first paragraph. Thus, the Examiner's enablement requirement for claims that have potential human therapeutic use seem to be directed to a standard of commercial efficacy/safety because of her repeated arguments that the plant extract may not be effective and/or non-toxic. Although clinical testing may eventually lead to the use of the *Ocimum gratissimum* extract as a therapeutic agent in humans, this type of rejection is tantamount to a requirement that the invention be in a commercially viable condition as of the filing date.

Secondly, Appellant submits that the Examiner has not provided any evidence to show that Vero and Molt4 cell lines (i.e. a mammalian and human T lymphoblast cell line, respectively) are non-acceptable in the art as an *in vitro* model that correlates to *in vivo* efficacy for the pharmacological activity of *Ocimum gratissimum*, i.e. inhibiting viral replication and the cytopathic effects of a virus in a cell.

In determining unpredictability, the burden rests initially with the Examiner to substantiate the unpredictability of the art and that the specification does not provide sufficient information to guide those of skill to make and use the claimed process across the full scope of the claims. In the instant case, a clear object is disclosed, namely inhibiting the cytopathic effects of a virus in a virus-infected cell by contacting the cell with an effective amount of an extract from *Ocimum gratissimum*. Examples are provided which describe the techniques necessary to use the plant extracts to exert their anti-viral activity through inhibition of viral replication and reduction in cytotoxicity in virus-infected cells (see the description at pages 7 to 31). While the specification focuses on mammalian and human cell lines (i.e. Vero and Molt4, respectively), there is no evidence that the description and examples provided therein are insufficient to guide a skilled person in applying the same techniques to other *in vitro* or *in vivo* models. Whatever unpredictability surrounds the use of further testing other than provided in Vero and Molt4 cells, the need for undue experimentation is diminished by Appellants' examples of how to make and use the method, including references cited therein to further aid the skilled person in practicing the invention as claimed. The Examiner has not submitted any evidence to dispute that the teachings in the specification could not be applied in numerous other embodiments. Accordingly, Appellant respectfully submits that the Examiner has not met the burden of providing evidence or reasoning sufficient to support a legal conclusion of lack of enablement for the subject matter claimed.

(iv) Predictability of in vitro data to in vivo test results.

(a) Hoggard et al., Havlir et al. and King et al.

In the Appeal, Appellant argued that it is well established under U.S. patent law and practice that *in vitro* results regarding a particular pharmacological activity can be predictive of *in vivo* test results if there is a reasonable correlation therebetween. Three publications (i.e. Hoggard *et al.*, Havlir *et al.* and King *et al.*) representative of the state-of-the-art and research relating to the field of anti-viral therapies were presented with the Appeal which demonstrated that *in vitro* results can be predictive of *in vivo* efficacy. For example, referring to King *et al.*:

- page 1640, 2nd column, last paragraph:

  ...data from in vitro enzyme- and cell-based systems have led to the prediction that the combination of AZT and stavudine (d4T) may be less efficacious than either compound alone due to the antagonistic effect that the combination has on the cellular thymidine kinase (13, 20, 28). Recently, this was found to be true in the clinical setting, in which HIV-1-infected patients responded better to monotherapy with d4T than to combination therapy with d4T and AZT (11). [Emphasis added.]

- the end of the 2nd column at page 1643 to page 1644:

  In vitro drug interaction studies have shown that NNRTIs can act synergistically with an NRTI to inhibit HIV-1 RT activity and/or HIV-1 replication (1,3,4). In clinical studies, combinations of an NNRTI with one or more NRTIs result in significant improvements in patients' clinical markers (7,9,26).

- page 1645, 1st column, 1st full paragraph:

  It is unknown if our in vitro observations of the antagonistic action of efavirenz plus another NNRTI would translate to antagonistic action in the clinical situation; however, there is precedence for these in vitro models to be predictive of the clinical situation (11, 13)...HIV-1 infected patients who were treated with the combination showed greater declines in CD4-cell count and lesser decreases in plasma HIV-1 RNA levels from the baseline levels than patients who were treated with d4T. Thus, in this case, the in vitro model was predictive of the clinical outcome. [Emphasis added.][3]

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3 **(1)** Balzarnin, J. *et al.* **1996**. Mol. Pharmacol. 49:882-890. **(3)** Carroll, S.S. *et al.* **1994**. J. Biol. Chem. 269:32351-32357. **(7)** D'Aquila, R.T. *et al.* and the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group Protocol 241 Investsigators. **1996**. Ann. Intern. Med. 124:1019-1030. **(9)** Freimuth, W.W. **1996**. p. 279-289. In J. Mills, P.A. Volberding, and L. Corey (ed.), Antiviral chemotherapy 4: new directions for clinical application research. Plenum Press, New York. N.Y. **(11)** Diane V. Havlir *et al.* 2000. The Journal of Infectious Diseases 182:321-325. **(13)** Patrick G. Hoggard *et al.* **1997**. Antimicrobial Agents and Chemotherapy 1231-1236. **(20)** Merrill, D.P. *et al.* **1996**. J. Infect. Dis. 173:355-364. **(26)** Staszewski, S., *et al.* 1999. N. Engl. J. Med. 341:1865-1873. **(28)** Zhu, Q.-Y., *et al.* **1996**. AIDS Res. Hum. Retrovir. 12:507-514.

In reply, the Examiner states:

> ...in the field of HIV, or viral therapy in general, there is no predictability to in vivo function when using in vitro tests only to establish that a drug has an effect on the virus...Appellants cite Hoggard *et al.*, Havilir *et al.* and King *et al.*...for the proposition that in vitro models can be predicative of the clinical situation when using combination therapy...The testing in the cited references differs from the instant in vitro assay because the individual compounds already had a proven track record of being tolerated by a patient population. In the instant invention the plant extract has not been shown to be to be [sic] effective against HIV in an individual.

Appellant respectfully submits that the primary issue is whether *in vitro* data correlates to *in vivo* results; not whether individual compounds necessarily have a proven track record of being tolerated by a patient population. The *in vitro/in vivo* correlation is not dependent upon a compound's track record. Rather it is the activity for which the compounds where tested in an *in vitro* model (e.g. antagonistic effect that the combination has on cellular thymidine kinase) and the observations made that led to a prediction that the compounds would be effective in the clinical setting.

Further, Appellant refers to El-Said *et al.*, which was cited by the Examiner on the grounds that the claims are inherently anticipated by this reference. Based on this reference, it is apparent that an extract derived from *Ocimum gratissimum* also has a proven track for "being well tolerated by a patient population" in view of the medicinal uses described therein for treating various ailments in the Nigerian community. Accordingly, the Examiner's argument that the compounds described in cited in Hoggard *et al.*, Havilir *et al.* and King *et al.* are known to be tolerated by a patient population does not undermine the potential pharmacological (or therapeutic) effect of the *Ocimum gratissimum* extract to work *in vivo*.

(b) Ayisi et al.[4]

Appellant submitted a post-filing publication by the inventor to show that persons skilled in this art would equate *in vitro* activity of anti-viral compounds described in the present specification with *in vivo* efficacy in inhibiting viral replication in cells. This paper discloses the results of a study in which the effects of *Ocimum gratissimum* (and other plant extracts) on *in vitro* HIV-1 and HIV-2 replication were compared to AZT. Using AZT as a point of reference, in light of its relative acceptance and success as a viral inhibitor in AIDS therapy, the results support the therapeutic potential of the anti-viral plant extracts. Thus, Applicant respectfully submits that *in vitro* testing of *Ocimum gratissimum* set forth in the instant specification (and illustrated by Applicant's post-filing publication) would be accepted by those skilled in the art as providing a reasonable correlation to inhibiting viral replication *in vivo*.

In reply, the Examiner states:

> ...the comparison of AZT in an in vitro environment with the plant extract in the in vitro environment cannot provide the correlation to establish that the plant extracts would work in the same manner as AZT would work in the in vivo environment...The experimental results in the cited reference and the results show [sic] in the instant specification does not provide any insight into whether the plant extracts can be administered to a patient at high enough concentration to be effective and to not be toxic.

Appellant respectfully submits that the Examiner has not provided any evidence to substantiate her allegation that the anti-viral effects of AZT and the *Ocimum gratissimum* extract shown in the same *in vitro* setting would not correlate to an *in vivo* result for the plant extract based on AZT's established therapeutic effect. In fact, the results of the comparative study support a

4 Nana K. Ayisi *et al. Comparative in vitro effects of AZT and extracts of Ocimum gratissimum, Ficus polita, Clausena anisata, Alchornea cordifolia, and Elaeophorbia drupifera against HIV-1 and HIV-2 infections.* Antiviral Research (2003) 58:25-33.

prediction that the plant extracts have potential to inhibit viral replication at the clinical level. Referring to MPEP §2164.03, it states:

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:
>
> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Emphasis added.]

Appellant maintains that successful *in vitro* testing for a particular pharmacological activity, as in the instant case, establishes a significant probability that *in vivo* testing for the same pharmacological activity will likely be successful. The exemplified mammalian cell lines Vero and Molt-4 are well known and art-accepted model systems that provide characteristics suitable for testing the ability of the plant extracts to inhibit HIV production in chronically infected cells, thereby reducing HIV cytopathicity.

(v) Enablement

Previously, Appellant argued that the Examiner's analysis of the enablement requirement is incomplete and has focused almost exclusively on, and given undue weight to, statements of unpredictability in the art, to support the inability of the *in vitro* model described in the instant application to be correlated to *in vivo* results.

In reply, the Examiner states that the unpredictability of the efficacy of the plant extract for the treatment of HIV is based on the use of the infusion of *Ocimum gratissimum* as described in El-Said *et al.* The Examiner makes the observation that Africa remains the center of the global HIV infection and rates of infection in the population are higher than anywhere else in the world. On this basis, were an extract of *Ocimum gratissimum* effective in treating HIV, then perhaps this would have been discovered some time ago in light of the long-term and well established medicinal use of the plant in the African community. The Examiner further speculates that the effective ingredient of the extract cannot get to the site of HIV viral infection at a high enough concentration to be effective to treat HIV in a patient.

Appellant presumes that the Examiner's position is therefore that it would require undue experimentation for a skilled person to practice the method in order to treat HIV viral infection in any individual. On this basis, Appellant's comments made above apply here as well (referring to subsection (i) *Therapeutic effect of Ocimum gratissimum.*) in asserting that it would not required undue experimentation to practice the invention based on the specification as of the filing date. Furthermore, a major reason for epidemic proportions of HIV is that a majority of carriers are asymptomatic for a few years. They don't show signs of the disease and often do not realize they are infected. During this asymptomatic period, HIV is actively multiplying, infecting and killing cells in the immune system.

Accordingly, Appellant submits that the claims are enabled because: (1) the claims define a method for inhibiting the cytopathic effects of a virus in a cell, not a therapeutic use in the treatment of HIV in a patient; and (2) the Examiner has not provided any evidence to show that the specification would not enable one skilled in the art to make and use the method as claimed.

Issue 2. - 35 USC §102(b)

The Examiner maintains that the claims are inherently anticipated in view of El-Said *et al.* even though Appellant has argued that the reference does not disclose a method of using the *Ocimum gratissimum* extract to inhibit viral replication in a virus-infected cell and the cytopathic effect of a virus.

More specifically, the Examiner asserts that El-Said *et al.* disclose that an extract of *Ocimum gratissimum* has been used in Nigerian herbal medicine for the treatment of fevers. Fever is a symptom that is associated with a viral or bacterial infection as evidenced by the Merck Manual. The Nigerian patient may not have appreciated the nuance that a compound found in the plant actually has a cytopathic effect on a virus in a test tube. However, where a method of the prior art is performed on either the same population or a subset of the same population as the claimed method using the same material and methodology, the prior art inherently would achieve whatever desired outcome was discovered and claimed by application. The Examiner therefore maintains that the treatment of a viral infection using an extract of *Ocimum gratissimum* is anticipated by El-Said *et al.* because a patient having a fever caused by a virus would be practicing the claimed invention by drinking a decoction made from *Ocimum gratissimum.*

Appellant respectfully disagrees in light of the following comments.

In essence, the Examiner has used the Merck Manual as evidence in attempting to show that an inherent characteristic of an *Ocimum gratissimum* extract (i.e. to treat fever caused by a viral infection) is taught by El-Said *et al.* which discloses that the same extract has been used to treat fever caused by a bacterial infection. Further, the Examiner states:

> Because fever is a symptom of a viral infection the treatment of fever by ingesting the extract plant comprises a method of contacting a virally infected cell with the extract. [Emphasis added.]

Fever is Controlled Through the Arachidonic Acid Pathway, not Viral Replication

Appellant submits that this statement is scientifically incorrect and that a skilled person would not recognize that in view of the prior art, an extract of *Ocimum gratissimum* inhibits viral replication. Bacteria/viruses produce endotoxins which stimulate host cells to produce cytokines called endogenic pyrogens. Endogenic pyrogens centrally affect the thermosensitive neurons in the hypothalamus to increase the production of heat and decrease in heat loss (i.e. febrile response). The cytokines also activate the arachidonic acid pathway. This pathway, as it relates to the febrile response, is mediated by several enzymes which release prostaglandin E2 (PGE2). Drugs that reduce fever (e.g. an extract of *Ocimum gratissimum*), are known as antipyretics (e.g. acetaminophen, ibuprofen) and work to inhibit prostaglandin synthesis thus, stopping the generation of PGE2.

The following passage has been taken from http://encyclopedia.thefreedictionary.com, which explains the mechanism of, and treatment for, fever:

> **Mechanism**
>
> Fever is a positive feedback mechanism which acts towards the direction of change (as opposed to negative feedback which acts opposite to change to maintain homeostasis). Therefore, fever is the opposite of thermoregulation. Substances which induce fever are called *pyrogens*. Although external pathogens may be the ultimate reason for a fever, it is the internal or endogenous pyrogens that ultimately cause the increase in the thermoregulatory set-point.

One model for the mechanism of fever is the detection of lipopolysaccharide (LPS), which is a cell wall component of gram negative bacteria. An immunological protein called Lipopolysaccharide Binding Protein (LBP) binds to LPS. The LBP-LPS complex then binds to the CD14 receptor of a nearby macrophage. This binding results in the synthesis and release of various cytokine factors, such as interleukin 1, 6 and the tumor necrosis factor alpha. These cytokine factors are released into general circulation where they migrate to the circumventricular organs of the brain, where the blood-brain barrier is reduced. The cytokine factors bind with endothelial receptors on vessel walls, or interact with local microglial cells. When these cytokine factors bind, they activate the arachidonic acid pathway. This pathway (as it relates to fever), is mediated by the enzymes phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2) and PGE2 synthase (membrane-associated protein involved in eicosanoid and glutathione metabolism, also known as mPEGS-1). These enzymes ultimately mediate the synthesis and release of prostaglandin E2 (PGE2).

PGE2 is the ultimate mediator of the febrile response. It acts near the ventromedial preopic area (VMPO) of the anterior hypothalamus and the parvocellular portion of the periventricular nucleus (PVH). It is in these areas that the thermal properties of fever emerge. Presumably, the elevation in thermoregulatory set-point is mediated by the VMPO, whereas the neuroendocrine effects of fever are mediated by the PVH, pituitary gland and various endocrine organs. Other heat effector mechanisms are mediated by the brain stem/medullary premotor sympathetic activation to the autonomic nervous system, which ultimately leads to the activation of brown adipose Tissue. The body can also induce shivering, or raise blood pressure through a mechanism of vasoconstriction.

The set-point temperature of the body will remain elevated until PGE2 (through ultimately the foreign pathogen) is no longer present.

Treatment

Drugs that reduce fever are known as antipyretics. Common antipyretics are acetaminophen, also called paracetamol, and NSAIDs such as ibuprofen. These drugs act on the cyclooxygenase enzyme used to create prostaglandin E2 synthesis. Therefore, they work as prostaglandin synthesis inhibitors, stopping the creation of PGE2. Vasopressin is also a potential antipyretic, which is released from the Hypothalamus to the posterior pituitary gland, where it then acts on the body through the bloodstream. [Emphasis added.]

Therefore, although fever is a symptom of a viral infection, ingesting the plant extract to reduce fever does not comprise a method of contacting a virally infected cell with the extract as alleged by the Examiner. Based on scientific principles, it can be held that whether for a viral or bacterial infection, an extract of *Ocimum gratissimum* can be expected to reduce fever by working through the arachidonic acid pathway to inhibit the generation of PGE2, and not through preventing viral replication.

Viral Incubation Period is Asymptomatic

Furthermore, during most virus infections, no signs or symptoms of disease occur through the stage of virus propagation. Thus, the incubation period (the time between exposure to the virus and onset of the disease) extends from the time of infection through the phase of propagation, ending when virus replication in the target organs causes disease. Every viral disease has a certain incubation period, the period between exposure to the virus and the development of symptoms. The incubation period for HIV can be as long as 20 years, which is why it is considered as a silent killer. There are four stages in HIV infection:

(1) Acute HIV infection. An illness similar to mononucleosis or the flu develops 2-8 weeks after initial HIV infection;

(2) Asymptomatic HIV infection. During this phase (which may last several years), **a person will test positive for HIV but will have no symptoms**;

(3) Persistent generalized lymphadenopathy. During this phase, swollen lymph glands are present.; and

(4) Opportunistic infections and cancers take effect, including AIDS.[5]

Appellant refers to the Appeal Brief in which the results of the Ayisi *et al.* paper were discussed insofar the effectiveness and observed mode of action by which the *Ocimum gratissimum* extract exerts its anti-viral effect compared to AZT, i.e. early as opposed to late viral event of HIV replication. Based on these results and the state of the art, it could be understood that the degree of efficacy of any particular anti-viral agent will likely depend on its target and/or the stage of the viral infection at which the agent is applied. Therefore, the Examiner's assertion that taking the *Ocimum gratissimum* extract to reduce fever would inherently inhibit viral replication is unfounded as these events (i.e. incubation and symptomatic phases) occur at different stages of the viral life cycle.

As a final note, the basis for the Examiner's rejection of the claims for inherent anticipation and for lack of enablement are contradictory. More specifically here, the Examiner argues that taking the *Ocimum gratissimum* extract to reduce fever would inherently inhibit viral replication. Alternatively, the Examiner doubts that the claims are enabled to treat HIV because "the effective ingredient of the *Ocimum gratissimum* extract cannot get to the site of HIV viral infection at a high enough concentration to be effective to treat HIV in a patient." Nevertheless, both arguments are unsound in view of the scientific principles discussed above. A method of inhibiting viral replication using the *Ocimum gratissimum* extract is not inherently anticipated by the prior art because the an antipyretic effect exerted by the extract is through inhibition of prostaglandin synthesis, and not viral replication. Further, lack of enablement is not an issue insofar as doubting whether the *Ocimum gratissimum* extract can reach the site of HIV viral

5 This information is widely available and may be found at numerous sources, including the National Center for Infectious Diseases at http://www.cdc.gov/ncidod/.

infection because the symptoms indicative of HIV (e.g. fever) are not exposed until long after the virus has already infected and propagated within the host.

In summary, Applicant respectfully submits that the invention, as claimed, is novel and patentably distinguishable over the prior art.

Relief Requested

In view of the foregoing, the Applicant requests that the appeal be allowed.

Respectfully submitted,

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